UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/678,765 | 10/02/2003 | George N, Serbedzija | 018852-000511US | 1627 |

20350 7590 11/14/2008

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| BERTOGLIO, VALARIE E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 11/14/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/678,765 | SERBEDZIJA ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *31,33,35-40 and 42-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33,35-40 and 42-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/05/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's reply dated 07/30/2008 has been received. Claims 1-30,32,34 and 41 have been cancelled. Claims 31,35-40,42-46 have been amended. Claims 47-57 are added. Claims 31,33 and 35-40 and 42-57 are pending and under consideration in the instant office action.

### *Priority*

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) was denied as set forth at page 4 of the office action dated 08/03/2006. The effective filing date granted for the claims is **02/22/1999** based on support in US Application 09/255,397. '783 does not provide support for screening compounds by assaying for gene expression changes. Applicant has remarked that the issue of priority does not currently appear to be material to the grounds of rejection raised and will further address the issue if it becomes relevant in future proceedings.

### *Claim Rejections - 35 USC § 112-1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Scope of Enablement*

Claims 31,33 and 35-38 remain rejected and claims 54 and 56 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening an agent for toxic activity comprising administering an agent to a teleost in vivo, processing in vitro or in situ said embryo in a manner to detect expression of a protein or mRNA in a specific organ or tissue, and quantifying mRNA or protein expression, wherein a change in said mRNA or protein expression in comparison to that of a control teleost embryo not administered the agent is indicative of toxic activity of

the agent, does not reasonably provide enablement for screening an agent for a therapeutic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Applicant has amended claim 31 to include, in addition to screening for toxic activity of an agent in a first fish, screening for desired activity of the same agent in a second fish. The second fish is not required to have any phenotype. The specification does not provide enabling teachings and guidance necessary to know how to carry out screening for a desired therapeutic activity commensurate in scope with the claims.

Applicant's Remarks have been fully considered and are not persuasive. Applicant argues a therapeutic activity is claimed and such is defined in the specification as "any activity of…an agent…which diminishes or eliminates pathological signs or symptoms when administered to a subject

exhibiting said pathology" (page 8 of Remarks). However, the fails to specify any pathology for the fish used to screen a therapeutic activity and therefore is drawn to use of a wildtype teleost. Thus, any agent identified by the claimed methods is a 'potential' therapeutic. The presence of indicators of therapeutic activity as outlined at paragraph [0292] of the specification is not necessarily indicative that therapeutic activity weill be present in a disease state requiring therapy. Increase of a apoptotic marker in wildtype cells does not necessarily indicate an agent will be a therapeutic for cancer or any other pathology (see page 9, paragraph 2 of Remarks).

Applicants also provide arguments to more generally support screening for therapeutic activity concomitant or alongside screens for toxic activity. Applicant refers to paragraph [0212] teaching that "combined methods are useful in assessing multiple effects of an agent, including desired and undesired responses...[and that] the ability to assess multiple activities and responses in an animal due to the administration of the agent is of particular benefit in identifying potential therapeutic compound and assessing their side effect". In response, this paragraph of the specification, as well as paragraph [0259], is referring to assessing specific activities of cell death and angiogenesis activity along with toxic activity. Thus, the specification is not supporting generic screening for any therapeutic activity. Applicant refers to paragraph [0292] in support of the claimed methods, discussing that one of skill in that art would know how to specifically adapt for a particular therapeutic activity of interest the discussed generic methods of assessing effects of agents. However, it is noted that paragraph [0292], taken in context of preceding paragraph [0291], is not drawn to screening for therapeutic activity. Paragraph [0291] discusses 'pharmacologic' activity.

Thus, it appears that the specification does support assaying multiple activities of an agent. However, it is not clear that this guidance is relevant to screening for "therapeutic" activity. The specification supports screening apoptotic and angiogenesis activity of an agent as well as toxic activity (of which apoptotic activity can be toxic). The specification mentions assaying pharmacological activity

of agents. However, there is no nexus that any agent having a pharmacologic activity, i.e. angiogenesis, will necessarily be therapeutic as claimed. It is requested that when Applicant responds to the instant rejection, specific reference be made to the specification to facilitate determining the presence of descriptive support and enabling disclosure.

***Claim Rejections - 35 USC § 112-2nd paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following new rejection is necessitated by amendment.

The rejection of claims 31,33,35-40 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 42-46 remain rejected and claims 53 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Mizell [1997, IDS].

As set forth above, priority to US provisional applications 60/075,783 and 60/100,950 for the instantly claimed subjected matter has been denied. The effective filing date is 02/22/1999.

Claim 42 is drawn to a method of screening an agent for toxic activity in vivo comprising administering an agent to a teleost and detecting a change in expression of a protein in a specific organ or tissue of the teleost, a response in the teleost indicating toxic activity in the tissue. Claim 43 requires that toxic activity be detected over time. Claim 44 requires that the response be detected in at least two tissues. Claim 45 requires that the response is over time at predetermined intervals. Claim 46 requires simultaneous testing of at least 2 teleosts.

Mizell taught a method for screening an agent for toxic activity in both zebrafish and medaka, which are teleosts that have a chorion. Mizell taught administering the agent (TCDD, toluene, benzene) to multiple (claim 46) dechorionated zebrafish embryos and detecting toxic effects by monitoring CYP1A activity (see page 416, last paragraph-page 416, paragraph 2, page 419, col. 2, paragraph 2; see Table 5, line 2 at page 96 of the specification). Early activation of CYP1A was shown as an indicator of TCDD toxicity. Multiple embryos were assayed at a time (page 421, col. 2, paragraph 4), meeting the limitations of claim 46. Mizell taught that toxic activity is detected after a 30 minute exposure to TCDD (page 415, col. 2, paragraph 2), which constitutes detecting toxicity over time at a predetermined interval as required by claims 43 and 45. Mizzel observed changes in heart formation as well as Cyp1A activity in both the gut and liver, fulfilling the limitations of claim 44.

Applicant argues that claim 42 now requires administering the test agent through the culture media and that Mizzel taught use of a single drop and placing the embryo in the drop for 30 min. Applicant argues this does not meet the limitation of administering the agent through the culture media. This argument is not persuasive. The agent is administered in 250µl of ERS or embryo rearing solution (page 422, col.2, paragraph 1), which is culture media. The only difference is that Mizzel did not use multi-well dishes but placed the media on parafilm in a petridish where surface tension kept each sample separate as opposed to the physical vbarriers of a petridish. The medium containing the agents and the volume were consistent with that of the instant invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

.

1) The rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Mizell (1997) in view of Maccubbin (1986, Aquatic Toxicology, 9:277-286) or Black (1988, Aquatic Toxicology, 11:129-142) or Marty *et al*, (1990, Aquatic Toxicology, 17:45-62) is rendered moot by the cancellation of the claim.

2) Claims 47-48 remain rejected and claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mizzel (1997) as applied to claims 42-46 above, and further in view of Terse [1993, Toxicon, 31:913-919].

Applicant's arguments regarding Maccubbin, Black and Marty are not relevant to this rejection (see page 12 of Remarks).

Mizell taught placing each embryo in a single droplet of medium in a single large Petri dish (page 421, col 2, paragraph 4). Mizell did not teach placing each embryo in a well of a multi-well plate (claim 47) wherein the volume of the wells is 300 microliters or less per well (claim 48).

However, Terse et al. taught screening the toxic activity of various mycotoxin agents using 96-well multi-well plates. As evidenced by the specification, standard 96-well plates have a volume of 300 microliters (see page 88, lines 27-29).

Applicant argues that none of the references cited discuss a method in which the test agent is added to the culture media. In response, as set forth above, Mizzell taught adding the agent to ERS, which is culture media. The amount of culture media is on par, or even within the range recited in the claims.

3) The following new rejection is necessitated by the addition of new claims.

Claim55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mizell (1997) in view of Maccubbin (1986, Aquatic Toxicology, 9:277-286) or Black (1988, Aquatic Toxicology, 11:129-142) or Marty *et al*, (1990, Aquatic Toxicology, 17:45-62).

Claim 55, depending from claim 42, is drawn to a method of screening an agent for toxic activity in vivo comprising administering an agent to a teleost *with a chorion*, and detecting a change in expression of a protein in a specific organ or tissue of the teleost, a response in the teleost indicating toxic activity in the tissue.

As set forth above, Mizell taught a method for screening an agent for toxic activity in teleosts. Mizell taught administering toxins to zebrafish embryos and detecting toxic effects by monitoring CYP1A activity as an indicator of toxicity. Mizell taught use of dechorionated embryos and did not teach leaving the embryos in the chorion during agent administration.

However, Maccubbin taught a method for screening an agent for toxic activity in rainbow trout, which is a teleost that has a chorion. Maccubbin taught administering 4 different carcinogens (agents) in DMSO to 50-100 (claim 46) embryos *within chorions* and detecting toxic effects by monitoring survival (see para bridging pages 279-280). Maccubbin taught that DMSO, given its widely recognized membrane penetration properties, can facilitate the passage of agents across the chorion, facilitating the screening for toxicity of agents by being a noninvasive technique, not requiring removal of the chorion. Maccubbin taught applying this technique to automate screening and for use in other species.

Similarly, Black taught application of chemicals to trout embryos by the method of Maccubbin and establishes while not all chemicals will be most efficiently transported across the chorion (egg shell), this method has advantages such as being noninvasive and has the ability to be automated and reproducible dose-response toxicity data should be readily obtainable (paragraph bridging pages 137-138).

Additionally, Marty *et al* showed the uptake of a variety of chemicals through the chorion of medaka using radiolabeled chemicals.

It would have been obvious at the time of filing to combine the teleost screening methods of Mizzel with the knowledge of Maccubbin, Black or Marty demonstrating that toxicity of compounds can be tested in teleost embryos with the chorion intact. One of skill in the art would have been motivated to not dechorionate the embryos prior to introducing an agent as it would allow for high throughput, automated and noninvasive screening. Loss of embryos in the dechorionation process would be prevented and time would be saved.

One would have a reasonable expectation of success in applying the screening techniques of Mizzel to embryos within their chorions as it was demonstrated in the art that many agents do cross the chorion to affect the embryo. While the chorion may offer some protection to the embryo, the art has demonstrated the chorion is not a complete barrier.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632